PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2004/001509	05.04.2004	04.04.2003

International Patent Classification (IPC) or both national classification and IPC
A61L24/04, A61L27/50, A61L24/06

Applicant
TA CONTRAST AB

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2004/001509

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 40

because:

☒ the said international application, or the said claims Nos. 40 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-23, 40

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1,2,6-12,14,16-19,23
	No:	Claims	3-5,13,15,20-22
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-23
Industrial applicability (IA)	Yes:	Claims	1-23
	No:	Claims	-

2. Citations and explanations

   see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Since claim 40 is directed to a method of treatment of the human or animal body by surgery, it relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. For the assessment of the subject-matter of present claim 40 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. Therefore, no opinion will be formulated with respect to the subject-matter of claim 40 (Article 34(4)(a)(i) PCT).

Re Item IV

Lack of unity of invention

The application lacks unity of invention as required by Articles 3(4)(iii) and 34(3)(a) PCT. The separate inventions are identified below:

1. Claims 1, 18 (completely), 6-17 (partially)
   Bone cement comprising a liquid monomer, a particulate polymer and a dissolved non-polymerisable organoiodine compound.

2. Claims 2, 19 (completely), 3, 6-17, 20 (partially)
   Bone cement comprising a liquid monomer portion comprising a polymerisable organoiodine compound and a particulate polymer comprising covalently bonded residues of a polymerisable organoiodine compound.

3. Claims 3, 6-17, 20 (partially)
   Bone cement comprising a liquid monomer portion and a particulate polymer, the liquid portion comprising a polymerisable organoiodine compound and/or the polymer comprising covalently bonded residues of a polymerisable organoiodine compound, wherein said polymerisable organoiodine compound comprises an organoiodine moiety covalently bonded via an amide but not an ester bond to a polymerisable moiety.

4. Claims 4, 5, 21-23 (completely), 6-17 (partially)
   Bone cement having a chemically homogenised distribution of all components therein.

5. Claims 24, 25, 36-39 (completely)
   Organoiodine compound of formula IV.

6. Claim 26 (completely)
   Method for producing a bone cement comprising admixing a liquid monomer portion and a particulate polymer portion under helium.

7. Claims 27-29 (completely), 32-35 (partially)
   Method for preparing a particulate polymer of a bone cement, wherein the polymer particles are formed by emulsion polymerisation.

8. Claims 30 (completely), 32-35 (partially)
   Method for producing polymer particles by emulsion polymerisation, characterised in that salts are added to the aqueous phase.

9. Claims 31 (completely), 32-35 (partially)
   Method for producing polymer particles by emulsion polymerisation, wherein the pH is adjusted by the addition of acids, bases or buffers.

10. Claim 41 (completely)
    Bone cement characterised in that the ultimate tensile strength and ultimate strain are greater than 10% higher than Palacos® bone.

The technical problem underlying the subjects 1-3 of the present application is the provision of improved radiopaque bone cements containing organoiodine compounds. Subjects 4, 6, 7 and 10 also relate to bone cements, but address different aspects such as the homogeneous distribution of all components in the cement, the provision of new organoiodine compounds or the improvement of the mechanical properties of the bone cements. Furthermore, these bone cements do not contain organoiodine compounds, so that it appears prima facie that there is no common special technical feature between these two groups of subjects, contrary to the requirements of Rule 13.1 and 13.2 PCT.

A further examination of the subjects 1-3 reveals three different solutions relating to radiopaque bone cements containing organoiodine compounds. The technical concept common to all three solutions is a bone cement comprising a liquid portion comprising a monomer, a particulate polymer portion and an organoiodine compound.

The document WO 99/62570 A discloses (cf. claims 1, 2, 16) a bone cement including a liquid component containing a polymerisable substance, a polymeric powder component and an organoiodine contrast medium.

In view of this document, the above-mentioned technical concept linking together the subjects 1-3 of the present application cannot serve as a special technical feature to establish a technical link in the sense of Rule 13.1 PCT between the subjects 1-3 of the present application.

No other features could be identified which could be considered as same or corresponding special technical features establishing a relationship between the subjects 1-3 (Rule 13.2 PCT). Hence, no general inventive concept underlying a unique invention (or a group of inventions) can be distinguished for claims 1-39 and 41.

In view of the absence of a single general concept between the different inventions, the present application lacks unity of invention. The different solutions not belonging to a common inventive concept are identified as the different subjects listed above. Each of the inventions is a distinct invention, characterised by its own special technical feature, defining the contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

Since the Applicant has paid the additional search fees for the inventions 2-4 indicated above, the following examination will be made with respect to the inventions 1-4.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents (D1-D5) cited in the International search report:

D1 ... WO 99/62570 A (Bone Support AB)
D2 ... US 6,040,408 A (Koole L. H.)
D3 ... Vázquez, B. et al., Biomaterials 20(21), pages 2047-2053 (1999)
D4 ... US 5,902,839 A (Lautenschlager E.P. et al.)
D5 ... EP 0 676 212 A (Bristol-Myers Squibb Company)

Invention 1:

Document D1 discloses (cf. claims 1, 2, 16) a method for preparing a bone cement comprising a non-polymerisable organoiodine compound with polymeric particles and a polymerisable substance.

The subject-matter of claims 1, 18 (completely) and claims 6-17 (partially) of the present application differs from D1 in that the non-polymerisable organoiodine compound is dissolved in either the liquid or the particulate polymer portion and is therefore novel according to Article 33(2) PCT.

Document D1, which is considered the most relevant state of the art, discloses (cf. page 3, lines 12-34 ; claims 1, 2, 16) a method for preparing a bone cement comprising a water-soluble, non-polymerisable organoiodine compound with polymeric particles and a polymerisable substance in order to prevent the cement obtained from releasing particles which contribute to the wear of bearing surfaces.

The objective technical problem underlying invention 1 of the present application is considered to improve the radiopaque bone cement of D1 in terms of mechanical strength of the polymer matrix of the set cement.

The solution in claim 1 of the present application is a bone cement comprising a monomer-containing liquid portion, a particulate polymer portion and a dissolved non-polymerisable organoiodine compound in at least one of said portions.

The subject-matter of claim 1 of the present application differs from D1 in that the non-polymerisable organoiodine compound is present in dissolved form instead of particles.

Since it is not apparent from the present application how this difference contributes to the solution of the above-defined technical problem, the subject-matter of claim 1 is not considered to involve an inventive step according to Article 33(3) PCT.

The same argument applies for the subject-matter of claims 6-18, as far as they depend on claim 1, so that the subject-matter of these claims cannot be considered as inventive either (Article 33(3) PCT).

Invention 2:

Document D2 discloses (cf. example 2 ; claims 1-5) a bone cement prepared with a copolymer of methyl methacrylate (MMA) and 2-[2'-iodobenzoyl] ethylmethacrylate and poly(methyl methacrylate) as solid component and MMA as liquid component.

Document D3 discloses (cf. page 2048, right-hand column, par. 1 ; page 2049, left-hand column, par. 3 - page 2050, left-hand column, par. 2) radiopaque acrylic cements prepared by incorporation of 2,5-diiodo-8-quinolyl methacrylate into the liquid phase of a PMMA bone cement as well as radiopaque acrylic cements prepared by addition of 2,5-diiodo-8-hydroxyquinoline to the solid phase for comparison.

The subject-matter of claims 2, 19 (completely) and claims 3, 6-17 and 20 (partially) differs from D2 and D3 in that both the liquid portion and the particulate portion comprise a polymerisable organoiodine compound and covalently bonded residues of a polymerisable organoiodine compound, respectively, and is therefore novel over D2 and D3 according to Article 33(2) PCT.

Document D2, which is considered the most relevant state of the art, discloses (cf. example 2 ; claims 1-5) a bone cement prepared with a copolymer of methyl methacrylate (MMA) and 2-[2'-iodobenzoyl] ethylmethacrylate and poly(methyl methacrylate) as solid component and MMA as liquid component.

In view of D2, the objective technical problem underlying invention 2 of the present application is considered to avoid the problems related to unreacted organoiodine monomer in the radiopaque bone cement.

The solution according to invention 2 is a bone cement comprising a liquid monomer portion comprising a polymerisable organoiodine compound and a particulate polymer portion, wherein the particulate polymer portion comprises covalently bonded residues of a polymerisable organoiodine compound.

The subject-matter of independent claims 2 and 19 differs from the closest prior art D2 in that the particulate portion of the bone cement comprises covalently bonded residues of a polymerisable organoiodine compound.

It is not apparent from the present application what technical effect (whether related to

the technical problem defined above or not) is achieved by the incorporation of covalently bonded residues of a polymerisable organoiodine compound into the particulate polymer portion of the bone cement. Consequently, the subject-matter of claims 2 and 19 is not considered to involve an inventive step according to Article 33(3) PCT.

Invention 3:
Document D2 discloses (cf. example 2 ; claims 1-5) a radiopaque bone cement prepared with an acrylate monomer containing organoiodine moieties covalently bonded to the acrylate monomer via ester or amide bonds.
This document is novelty-destroying for the subject-matter of claims 3 and 20 of the present application (Article 33(2) PCT).

Document D3 discloses (cf. page 2048, right-hand column, par. 1 ; page 2049, left-hand column, par. 3 - page 2050, left-hand column, par. 2) radiopaque acrylic cements prepared by incorporation of 2,5-diiodo-8-quinolyl methacrylate into the liquid phase of a PMMA bone cement as well as radiopaque acrylic cements prepared by addition of 2,5-diiodo-8-hydroxyquinoline to the solid phase for comparison.
The subject-matter of claims 3, 6-17 and 20 (partially) differs from D3 in that the polymerisable organoiodine compound comprises an organoiodine moiety covalently bonded via an amide bond to a polymerisable moiety and is therefore novel over D3 according to Article 33(2) PCT.

Document D2, which is considered the most relevant state of the art, discloses (cf. example 2 ; claims 1-5) a radiopaque bone cement prepared with an acrylate monomer containing organoiodine moieties covalently bonded to the acrylate monomer via ester or amide bonds.

In view of D2, the objective technical problem underlying invention 3 of the present application is considered to provide an alternative radiopaque bone cement which avoids the release of organoiodine compounds with unclear physiological compatibility due to cleavage of ester bonds.

The solution according to invention 3 is a bone cement comprising a liquid monomer

portion and a particulate polymer, the liquid monomer portion comprising a polymerisable organoiodine compound and/or the particulate polymer comprising covalently bonded residues of a polymerisable organoiodine compound, wherein said polymerisable organoiodine compound comprises an organoiodine moiety covalently bonded via an amide but not an ester bond to a polymerisable moiety.

The additional technical features in claims 6-17 (partially) of the present application do not contribute to the solution of the technical problem formulated above, so that the subject-matter of claims 6-17 (partially) cannot considered to involve an inventive step according to Article 33(3) PCT.

Invention 4:

Document D4 discloses (cf. claims 1-4, 6-8) an all-liquid bone cement product consisting of a plurality of liquid components in separate containers to be mixed and reacted together to produce a polymerised bone cement. The solutions contain poly(methyl methacrylate), methyl methacrylate and optionally finely-divided particles of a radiopacifier. Since all components are in liquid form, the resulting bone cement has a chemically homogenised distribution of the components and this disclosure is novelty-destroying for the subject-matter of claims 4, 5, 21, 22 (completely) and claims 13, 15 (partially) of the present application according to Article 33(2) PCT.

Document D5 discloses (cf. col. 3, lines 32-43) a bone cement mixture including poly(methyl methacrylate) in powder form and methyl methacrylate as a liquid monomer. The resulting bone cement consists of poly(methyl methacrylate) and has therefore a chemically homogenised distribution of the components.
D5 takes away the novelty of claims 4 and 21 of the present application (Article 33(2) PCT).

Document D4, which is considered the most relevant state of the art, discloses (cf. claims 1-4, 6-8) a bone cement having a chemically homogenised distribution of the components therein, obtained by polymerisation of several solutions containing dissolved poly(methyl methacrylate), methyl methacrylate and optionally finely-divided particles of a radiopacifier.

In view of D4, the objective technical problem underlying invention 4 of the present application is considered as to provide an alternative radiopaque bone cement having a chemically homogenised distribution of the components therein.

None of the additional technical features in the novel dependent claims 6-12, 14, 16, 17 (partially) and claim 23 (completely) of the present application contributes to the chemically homogenised distribution of the components in the bone cement. Consequently, no inventive activity can be acknowledged for the subject-matter of claims 6-12, 14, 16, 17 (partially) and claim 23 (completely) (Article 33(3) PCT).